ADHD: can reinforcement resolve the problem?

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CHAPTER 1

General Outline and Statement of The Problem

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a chronic childhood developmental disorder, with symptoms of inattentiveness, hyperactivity, and impulsivity (American Psychiatric Association APA, 2000). A recent review and meta-regression analysis suggests that the overall pooled worldwide prevalence of ADHD is 5.3%, affecting more boys than girls in a ratio of 4:1 (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). The disorder severely disrupts daily life functioning, impairing social, professional as well as family functioning (Barkley et al., 2006; Biederman, Faraone, Spencer, Mick, Monuteaux, & Aleardi, 2006). The prognosis of ADHD is poor: Children with ADHD show increased risk for developing psychiatric or personality disorders as adolescents or adults (Biederman, Monuteaux, et al., 2006; Spencer, 2006). Although the diagnoses continues to be targeted as non-existent or a 'fashion-diagnosis' in the media, a consensus statement signed by more than 70 world-wide experts in the field points to the validity of the diagnosis and its adverse impact on the lives of those diagnosed with ADHD (International consensus statement on ADHD, 2002).

Three subtypes of ADHD have been defined: an inattentive subtype, a hyperactive/impulsive subtype and a combined subtype (APA, 2000). Inattentiveness has been recognized as difficulties with close attention to details, careless mistakes, problems with sustained concentration, daydreaming, frequent shifts in uncompleted activities, difficulties in organizing, chaotic behaviour, being easily distracted by irrelevant stimuli, and forgetfulness. Hyperactivity may manifest itself in restlessness, squirming in one's seat, excessive running, climbing, excessive talking, and being often 'on the go'. Impulsivity is manifested by impatience, difficulty in delaying responses, blurting out answers, difficulty awaiting turns, frequent interruptions on others, and behaviour that may lead to accidents (APA, 2000). Symptoms must be (1) present before the age of 7, (2) pervasive across situations, and (3) impair the child's social and academic functioning.

One of the major issues in identifying the symptoms that are associated with ADHD is the highly variable occurrence of these problems. The fourth revised edition of the Diagnostic and Statistical Manual of Mental Disorders, (DSM-IV-TR) states that the problems with attention and hyperactivity/impulsivity are variable across situations and worsen, when tasks require sustained attention or mental effort, or when tasks lack intrinsic appeal or novelty (APA, 2000). This abnormal response to environmental factors in ADHD has also been observed in an aberrant sensitivity to reinforcement contingencies such as rewards and penalties (see Chapter 2). The increase in behavioural symptoms as a function of task difficulty or task attractiveness suggests that children with ADHD suffer from *motivational problems* that interfere with their behaviour. Motivational processes in humans involve the ability to assign values to objects in the environment, whereas one is tended to work for 'rewards', while avoiding 'punishment'. Motivational problems may, therefore, translate in to an abnormal response to monetary contingencies, such as observed in children with ADHD. Several theoretical frameworks on ADHD have incorporated this aberrant reinforcement sensitivity when explaining the disorder (Casey, Nigg, & Durston, 2007; Castellanos & Tannock, 2002; Douglas, 1989; Doyle et al., 2005; Frank, Scheres, & Sherman, 2007; Haenlein & Caul, 1987; Luman et al., 2005; Nigg, 2005; Quay, 1988a; Sagvolden, Johansen, Aase, & Russell, 2005; Sergeant, Oosterlaan, & Van der Meere, 1999; Sonuga-Barke, 2002; Tripp & Wickens, in press; Wallace & Newman, 1990). The nature of this problem, however, is not well understood.

The aim of the current thesis is to extend the present literature on reinforcement sensitivity in ADHD. By manipulating reward and penalties that are contingent on performance, there is investigated whether neurocognitive deficiencies that are associated with ADHD may be secondary to a motivational deficit such as aberrant reinforcement sensitivity. In addition, autonomic responses to reinforcement are investigated to obtain more insight into the underlying psychophysiological mechanisms.

Aetiology of ADHD

ADHD has been recognized as a disorder that can be explained by both biological as well as psychosocial factors. Recent work has shown that the genetic heritability varies between 60 to 90 percent (Faraone & Doyle, 2001; Faraone & Kahn, 2006; Li, Sham, Owen, & He, 2006; Waldman & Gizer, 2006). Candidate gene studies have identified several genes that are implicated as being (small) contributors to the aetiology of ADHD. Already at an early age, children with ADHD have been found to suffer from brain abnormalities, which emphasize a genetic or early environmental

cause of the disorder (Castellanos et al., 2002; Shaw et al., 2006). Neuroanatomically, there is evidence of smaller total volumes of the cortex of children with ADHD, involving both gray and white matter volume differences (Bush, Valera, & Seidman, 2005; Seidman, Valera, & Makris, 2005). Children with ADHD have been found to show smaller volumes in four specific areas of the brain: (a) the prefrontal cortex (PFC), (b) the corpus callosum, (c) the basal ganglia, and (d) cerebellum (Bush et al., 2005; Seidman et al., 2005). Most of these areas also function abnormally in children with ADHD, specifically the PFC, the anterior cingulate cortex (ACC), the basal ganglia and the cerebellum (see for review Casey et al., 2007). Furthermore, ADHD has been associated with alterations in catecholamine pathways, that may contribute to dysregulation of PFC circuits in this disorder (Arnsten, 2006; Oades et al., 2006). Environmental factors that have been identified as being associated with ADHD are smoking or drinking during pregnancy, maternal infections, or maternal stress (Talge, Neal, & Glover, 2007), complications during birth (premature birth) or low birth weight (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Linnet et al., 2006), or traumatic brain injury and stroke (Herskovits et al., 1999). Recent studies indicate that prenatal exposure to lead and smoking during pregnancy may activate the genes that have been related with ADHD (Neuman, Lobos, Reich, Henderson, Sun, & Todd, 2007; Swanson et al., 2007). In addition, several psychosocial factors relate with the development of ADHD such as early deprivation (Kreppner, O'Conner, & Rutter, 2001) and the absence of positive parenting (Chronis et al., 2007).

There are several pharmacological and behavioural interventions that have been demonstrated to affect positively the core features of ADHD, and to some extent social and academic functioning (Biederman, Spencer, & Wilens, 2004; Majewicz-Hefley & Carlson, 2007). The most utilized pharmacological intervention for ADHD is treatment with methylphenidate (MPH). MPH is a dopamine transporter antagonist that has been found to improve the behavioural symptoms of ADHD, as well as neurocognitive functioning (Solanto, Anrsten, & Castellanos, 2000) with relatively minor side effects (Rapport & Moffit, 2002). In addition, amphetamines and norepinephrine reuptake inhibitors (atomoxetine) were found to be effective in the treatment of ADHD (Biederman et al., 2004; Prince, 2006). The multi-model treatment (MTA) study on ADHD of the National Institute of Medical Health (NIMH) demonstrated greater effectiveness of pharmacological than behavioural interventions on ADHD symptoms as assessed by parents and teachers (Brown et al., 2005; Jensen, Arnold, Severe, Vitiello, & Hoagwood, 2004). A follow-up of the MTA study, however, demonstrated that the differences in the effectiveness of behavioural and pharmacological interventions diminished over time (Jensen et al., 2007). In addition, despite the benefits of pharmacological interventions, these therapies are unable to completely

ameliorate behaviour problems for all children with ADHD and there is no evidence that MPH improves academic achievement (Hoffman & DuPaul, 2000).

There is strong evidence of considerable comorbidity between ADHD and a number of disorders such as mood and anxiety disorders, anti-social behaviour disorder, learning disorder, motor coordination disorder and pervasive developmental disorder (Kadesjö & Gillberg, 1999; Pliszka, 1998; Spencer, 2006). Children with ADHD with comorbid disorders have been found to show poorer outcomes than children with ADHD-only in terms of social, emotional, and psychological difficulties (Spencer, 2006). For example, ADHD with comorbid conduct disorder (CD) is thought to represent a high risk condition with more severe behavioural problems and poorer prognosis than ADHD or CD alone (Faraone et al., 1998).

An Abnormal Sensitivity to Reinforcement Contingencies?

Several experimental studies have shown that the outcome of the ADHD symptoms may differ, depending on the environment. Research in the 1980's demonstrated that children with ADHD improved in performance when tasks were made more salient, novel, or interesting (Zentall, & Meyer, 1987; Zentall & Shaw, 1980). For example, when hyperactive children performed an attention task, performance was impaired when the child was alone or solely in the presence of the mother, in contrast to when an experimenter was present (Draeger, Prior, & Sanson, 1986; Gomez & Sanson, 1994; Power, 1993). Behavioural activity of children with ADHD diminished more than typically developing children when they saw a (stimulating) cartoon versus a neutral film (Antrop, Buysse, Roeyers, & Van Oost, 2002). Similarly, stimulating children with ADHD with visual cartoons compared to no stimulation normalized their difficulty with waiting (Antrop, Stock, Verte, Wiersema, Baeyens, & Roeyers, 2006). This environment-behaviour interaction has been confirmed in studies that demonstrate an abnormal behavioural sensitivity to contingencies such as reward and punishment (see Chapter 2 of this thesis). These findings point towards motivational problems in ADHD that come to the fore in lower self-rated motivation compared to healthy individuals, preference for easy work, less enjoyment of learning, less persistence, and a greater reliance on external than on internal standards to judge their performance (Carlson, Booth, Chin, & Canu, 2002). An important question is to what extent these problems interfere with the behavioural and intellectual abilities of children with ADHD. One method to study this is to investigate the impact of reinforcement contingencies, such as reward and response cost, on neurocognitive performance of children with ADHD.

The concept of motivation relates to the question of how organisms make choices (see Chapter 4), direct behaviour, and plan actions on the basis of internal evaluation processes regarding their environmental goals, passed experiences, and internal needs (Watts & Swanson, 2002). Humans tend to work for stimuli that are assigned as rewards, while they tend to avoiding aversive stimuli. Since all human behaviour is motivated (except for habits or basic automatic processing such as early visual processing), motivation, reinforcement and behaviour are deeply intermingled (Berridge & Robinson, 2003; Morgane, Galler, & Mokler, 2005). Berridge and Robinson (2003) reviewed the literature on the impact of reinforcement on psychological components and suggested that reward can have an impact on three major psychological components: motivation (wanting), learning, and emotion/affect (liking). The impact of reward on these components is associated with different circuits in the brain. Firstly, reward can increase the desire to want or do something (increasing motivation), which greatly influences behaviour. This is a largely automated process. In terms of task performance, a reward can increase the attention that is allocated to a task, which can increase performance (Sarter, Gehring, & Kozak, 2006). A meta-analysis on the impact of reward on children in classroom situations, demonstrated that by using positive reinforcement (verbal praise, rewards, presents or candy), the intrinsic motivation of children increased, which, in turn, increases performance (Cameron & Pierce, 1994). Secondly, reward can facilitate learning processes, since reward will likely increase the chance of the repetition of behaviour (Schultz, Dayan, & Montague, 1997; Wise, 2004). Otherwise, the omission of reward (or penalty) will decrease the chance of repetition. This process is mediated by dopamine responses to reward, which are suggested to 'stamp in' stimulus-response associations (Wise, 2004). Thirdly, motivation and learning are separated from the more conscious affective component of 'liking': Usually, a reward induces positive emotions such as happiness, while penalty will induce negative emotions such as anxiety.

If children with ADHD suffer from an abnormal sensitivity to reinforcement such as reward or penalty, children with ADHD may show abnormal changes in performance in face of contingencies, show problems with reinforcement learning, show abnormal emotional responses to reinforcement; in this thesis, the first two components are investigated.

Psychophysiological Markers of Abnormal Reinforcement Sensitivity

Children with ADHD have been found to show abnormal psychophysiological responses to reward and penalty, such as abnormal heart rate or skin conductance changes (e.g., Crowell, Beauchaine, Gatzke-Kopp, Sylvers, Mead, & Chipman-Chacon, 2006). While skin conductance responses are mainly controlled by the sympathetic nervous system (SNS), heart rate changes are controlled by both SNS as well as the parasympathetic nervous system (PNS, Brownley, Hurwitz, & Schneiderman, 2000). The SNS and PNS are both part of the autonomic system that plays an important role in regulating physiological arousal and activation, to make the system ready for appropriate behavioural responses (Gray, 1982; 1988; Panksepp, 1982; Porges, 1995). Since reinforcement influences the autonomic system, which activates behavioural changes, studying this system in ADHD may provide more insight into abnormal reinforcement sensitivity.

Sensitivity to Reward and Punishment

According to Gray (1982, 1988) behaviour is modulated by motivational factors through two separate brain systems that are responsible for either behavioural activation (approach behaviour or active avoidance) or behavioural inhibition (extinction behaviour or passive avoidance). Rewards or non-punishment activate the appetitive system (behavioural activation system, BAS), which initiates behaviour and relates to feelings of hope and relief. Aversive stimuli or non-rewards, inhibit (ongoing) behaviour and relate to feelings of anxiety (behavioural inhibition system, BIS). Psychophysiological evidence suggests that both the BIS and the BAS are dominated by the sympathetic nervous system. Gray (1988) suggested that the meso-limbic dopamine pathway, including the ventral tegmental area and ventral striatum, dominates the BAS, which is implicated in mobilizing energy and *increasing heart rate* (Fowles, 1980, 1988). The BIS is controlled by the septo-hippocampal system and is closely related to the Papez loop that depends on noradrenalin and serotonin (Fowles, 1980, 1988). According to Fowles, *increased skin conductance responses* are found to represent activity in the BIS. In addition to the BIS and BAS, Gray (1988) suggested that behaviour is regulated by flight/fight reactions to the perception of immediate danger or rewards, which includes activation of the amygdala (Panksepp, 1982). According to Porges (1995) the activation of the fight/flight system is dependent on (complete withdrawal of) the PNS.

Various psychiatric illnesses have been suggested to be the results of a distortion in the interaction between the BIS, BAS and parasympathetic activity (Beauchaine,

Katkin, Strassberg, & Snarr, 2001). Quay (1988a; 1988b; 1988c; 1997) argued that the behaviour that characterizes children with ADHD (inattentiveness, hyperactivity and impulsivity) is a consequence of an imbalance between BIS and BAS functioning. Children with ADHD would suffer from a weak BIS, resulting in decreased inhibition of initiated responses and an inability to detect and respond to stimuli that signal punishment. Alternatively, Newman (Newman, 1987; Patterson & Newman, 1993; Wallace & Newman, 1990) proposed that ADHD is largely related to the dominance of the BAS over a weak BIS, suggesting that disinhibited behaviour is the result of a lack of attention to signals of penalty in the presence of a reward signal. If Quay (1988a; 1988b; 1988c; 1997) is correct, children with ADHD would display a decreased autonomic sensitivity to penalty, indicating a low BIS, while the suggestions of Newman (Newman, 1987; Patterson & Newman, 1993; Wallace & Newman, 1990) would indicate an additional increased response to instances of reward, indicating a strong BAS over a weak BIS. The studies that investigated BIS and BAS functioning in ADHD yield heterogeneous results. There is some evidence of a weak BIS in ADHD, since ADHD has been associated with reduced noradrenalin precursors (Rogeness et al., 1989) and ADHD groups exhibited reduced urinary noradrenalin metabolites (Sherkim, Dekirmenjian, Chapel, & Davis, 1982; Shekim, Sinclair, Glaser, Horwitz, Javaid, & Bylund, 1987; Yu-cu & Yu-feng, 1984). In addition, ADHD has been associated with low baseline skin conductance activity (Beauchaine et al., 2001) as well as smaller skin conductance reactivity during stress (Boyce, Quas, Alkon, Smider, Essex, & Kupfer, 2001; Van Lang, Tulen, Kallen, Rosbergen, Dieleman, & Ferdinand, 2007; Zahn & Kruesi, 1993). This would confirm low SNS activity in ADHD, although other studies of skin conductance activity in ADHD did not demonstrate these effects (Herpertz et al., 2001; 2003; 2005). No evidence was revealed for increased sympathetic activity to instances of reward that would suggest an overactive BAS (Beauchaine et al., 2001). Chapters 2, 3, 4 and 6 of this thesis investigate heart rate and skin conductance responses of children with ADHD to reinforcement contingencies such as reward and penalty. If children with ADHD suffer from a strong BAS and a weak BIS, larger autonomic responses to reward (or the omission of penalty) and smaller autonomic responses to penalty (or the omission of reward) are expected in children with ADHD compared to typically developing controls.

Heart Rate Variability

In order to maintain an optimal performance or recover from the performance effects of detrimental manipulations, an increase in attentional effort is required (see for review Sarter, Gehring, & Kozak, 2006). For example, when task become more difficult subjects should increase the attention allocation in order to perform well, since difficult tasks require more attention to process information and respond accurately than

easy tasks. This allocation of attention is suggested to be a physiological process and involves changes in electrophysiological brain activity (Barry, Clarke, & Johnstone, 2003) as well as changes in the autonomic system (Brownley et al., 2000; Critchley et al., 2003). The changes in sustained attention are suggested to reflect changes in the variability in heart rate, which are fluctuations in the beat-to-beat interval over a period of time (Hyde & Izard 1997; Mulder & Mulder, 1981). When tasks require active attention, the mid and low frequency (.04 - .15 Hz) fluctuations in heart rate are found to diminish, which is considered as a (primarily) sympathetic measure of task engagement (Brownley et al., 2000; Critchley et al., 2003; Jorna, 1992). A decrease in variability in these frequency bands has been associated with changes in metabolic activity in the brain, for example, when tasks become more difficult (Akselrod, Gordon, Madwed, Snidman, Shannon, & Cohen, 1985; Brownley et al., 2000; Critchley et al., 2000). Children with ADHD compared to typically developing children display an enhanced variability in the mid and low frequency heart rate bands when performing a cognitive task (Börger, Van der Meere, Ronner, Alberts, Geuze, & Bogte, 1999; Börger & Van der Meere, 2000), suggesting difficulties in the intentional control over the allocation of attention. Interestingly, the attention allocation increases not only when tasks become more difficult, but also when tasks are rewarded (Suess et al., 1998). Possibly, children with ADHD suffer from a motivational problem and require external stimulation such as reward and penalty to increase the allocation of attention that is necessary to maintain an optimal performance level (Douglas, 1989; Sergeant et al., 1999). If this is correct, children with ADHD are expected to show abnormal autonomic responses to contingencies such as reward and punishment in terms of low and mid frequency heart rate variability. This is investigated in Chapter 6.

Theoretical Frameworks of ADHD and Abnormal Reinforcement Sensitivity

Several theoretical explanations of ADHD have incorporated motivational problems as the core feature of the disorder (see Chapter 2 for a review), although the theoretical frameworks considerably differ in detail. Some have proposed a *smaller sensitivity to reinforcement* in ADHD: Children with ADHD would suffer from an elevated reward threshold that implies that children with ADHD need more rewards than controls in order to impact their behaviour (Haenlein & Caul, 1987). Similarly, according to a neurobiological model of ADHD (Sagvolden et al., 2005; Johansen, Aase, Meyer, & Sagvolden, 2002) a dysfunction in the dopamine transmission in the fronto-limbic circuitry is responsible for a faster decay of reward and a smaller effects of extinction. Quay (1988a; 1988b; 1988c; 1997) suggested that ADHD is characterized by a

smaller sensitivity to punishment rather than reward, which, according to Newman (Newman, 1987; Patterson & Newman, 1993; Wallace & Newman, 1990) is the result of increased attention that is directed to reward stimuli. Other models, however, have suggested a *greater sensitivity to reinforcement* in ADHD as expressed by increased frustration to the omission of rewards (Douglas, 1989). Sergeant, et al. (1999) and Van der Meere (2002) proposed that a *self-regulation deficit* is responsible for ADHD, which is expressed in a greater behavioural dependence on external reinforcement than on internal goals in ADHD. As a result, when testing the different models regarding an aberrant reinforcement sensitivity in ADHD, one needs to focus on whether children with ADHD are either abnormally sensitive to reinforcement in general (e.g., Sergeant et al., 1999), to the valence of reinforcement (Newman, 1987; Quay, 1988a; Sonuga-Barke, 2002), the magnitude of reinforcement (Haenlein & Caul, 1989) or the frequency of reinforcement (Douglas, 1989; Sagvolden et al., 2005). These four aspects of reinforcement are, therefore, investigated in the current thesis.

Neurocognitive Problems in ADHD: The Search for Endophenotypes

A recent approach in studying the mechanisms that may explain the behavioural and intellectual problems that characterize ADHD has been the search for endophenotypes (Almasy & Blangero, 2001; Castellanos & Tannock, 2002; Doyle et al., 2005; Gottesman & Gould, 2003; Waldman, 2005). Endophenotypes are predisposing (familiar) vulnerability markers that are correlated with the disorder and may explain the relation between the genotype (the genes) and the phenotype (the behavioural symptoms) (Gottesman & Could, 2003; Waldman, 2005). Identifying endophenotypes is useful, since ADHD is a complex disorder in the sense that there is a weak mapping between susceptibility genes and the behavioural symptoms of ADHD (Cornblatt & Malhotra, 2001). Interestingly, neuroanatomical dysfunctions in ADHD show correlations with both the genotype, as well as the fenotype that are larger than the direct correlation between the genotype and the phenotype. This has led researchers to conclude that endophenotypes should be solidly grounded in neuroscience in order to be useful (Castellanos & Tannock, 2002).

Structural and functional imaging studies have shown that three major brain pathways relate to the development of ADHD: the fronto-striatal system, the brain pathway that connects the basal ganglia with the prefrontal cortex, the fronto-cerebellar pathway that connects the cerebellum with the prefrontal cortex, and the fronto-limbic pathway that connects limbic structures such as the amygdala and ventral stria-

tum with frontal cortex (Arnsten, 2006; Castellanos & Tannock, 2002; Nigg & Casey, 2005). The neuroanatomical pathways have led researchers to postulate three neurocognitive endophenotypes that relate to the aetiology of ADHD: *cognitive control, temporal information processing* and an *abnormal sensitivity to reinforcement contingencies* (Bidwell, et al., 2007; Casey et al., 1997; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006, Castellanos & Tannock, 2002; Johansen et al., 2002; Nigg, 2005; Sagvolden et al., 2005).

The fronto-striatal and fronto-cerebellar pathway that connects the (dorsal) striatum and the dorsolateral prefrontal cortex (DLPFC), has been found to be implicated in *cognitive control functions* (or executive control functions) (Casey et al., 1997; Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Semrud-Clikeman, Steingard, Filipek, Biederman, Bekken, & Renshaw, 2000). Cognitive control is referred to as the ability to adjust flexibly and appropriately to continuous changing environmental demands in relation to internal goals or intentions (Norman & Shallice, 1986; Stuss, Shallice, Alexander, & Pictor, 1995) and is opposed to more automated processes (Posner & Petersen, 1990). Children with ADHD have been found to show cognitive control problems in four areas: working memory (holding information in mind), inhibition (suppressing ongoing motor responses), planning (organizing future action sequences), and interference control (ignore irrelevant information) (Pennington & Ozonoff, 1996; Sergeant, Geurts, & Oosterlaan, 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Furthermore, cognitive control problems in ADHD become evident in the impaired ability to discriminate between good and bad outcomes of responses (Itami & Uno, 2002; Toplak, Jain, & Tannock, 2005). Although there is there is general consensus that children with ADHD suffer from problems with cognitive control (Barkley, 1997; Bidwell, Willcutt, Defries, & Pennington, 2007; Castellanos & Tannock, 2002; Nigg, 2005), the mechanisms of these deficiencies remain unclear. In Chapters 2, 4 and 5 of the current thesis there is investigated whether cognitive control may be secondary to a motivational deficit such as an abnormal sensitivity to reinforcement.

In addition to cognitive control functions, the cerebellum and basal ganglia (both sub-cortical structures) are associated with *temporal information processing:* monitoring the timing of events (Haber, 2003; McClure, Berns, Montague, 2003; Spencer, Zelaznik, Diedrichsen, Ivry, 2003). Temporal information processing is critical for planning, the initiation and suppression of behaviour, but also for the organization of muscle-driven movements of the body (Haber, 2003; Castellanos et al., 2006). This function may therefore play a major role in problems such as motor-restlessness and clumsy behaviour of children with ADHD. Difficulties in temporal information

processing in ADHD are manifested in problems with time discrimination and time (re)production (Toplak, Dockstader, & Tannock, 2006). Children with ADHD seem to have an internal clock that runs too fast (resulting in time underestimations). In addition, problems with temporal organization of motor output are observed such as the well-known pattern of slow and variable responding (Leth-Steensen, Elbaz, & Douglas, 2000; Rubia, Smith, Brammer, & Taylor, 2007; Van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005a). Subcortical dysfunctions such as those related to temporal information processing are less obviously linked to motivational problems and in Chapter 3 such an attempt has been made by investigating time production performance under various motivational conditions.

Dysfunctions in the fronto-limbic pathway have been associated to problems in motivated behaviour, pleasurable sensations and reward approach (Berridge & Robinson, 2003; Gray, 1988; Schultz, 2000; Wise, 2004). This pathway connects the ventral striatum with the orbital frontal cortex (OFC) and ventral medial prefrontal cortex (VMedPFC; Haber, 2003; Zelazo & Mueller, 2002), which have close connections with the ACC. The input comes mainly from the amygdala and hippocampus. This pathway has been related to an *abnormal sensitivity to reinforcement contingencies* in ADHD (Castellanos & Tannock, 2002; Johansen et al., 2002; Nigg, 2005; Sagvolden et al., 2005). For example, children with ADHD compared to controls prefer immediate small over larger delayed gratification (Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Tripp & Alsop, 1999). Neuroimaging studies have demonstrated that children with ADHD show impaired activity in the ventral striatum during reward anticipation (Scheres, Milham, Knutson, & Castellanos, 2007) that may explain this preference for immediate reward.

The acknowledgement of several endophenotypes in ADHD highlights the importance of studying cognitive control, temporal information processing, and reinforcement deficiencies in concert.

Outline and Aims of the Current Thesis

The studies presented in the current thesis aim to extend the present literature on the role of reinforcement in ADHD. The impact of reward and penalty on neurocognitive performance as well as autonomic responses are studied, under the assumption that people are motivated to work for rewards, while avoiding punishment. Apart from the review of the literature (Chapter 2), around 200 children between 8 and 12 years old participated in the experimental studies (Chapters 3, 4, 5, and 6). In these stud-

ies children with ADHD were compared to typically developing children or a clinical comparison group (Chapter 5). **Chapter 2** reviews the literature on reinforcement sensitivity in ADHD. Five theoretical frameworks are discussed, as well as 22 experimental studies that investigated the impact of reinforcement in children with ADHD on neurocognitive performance, motivation, and autonomic responses. In **Chapter 3**, the impact of reinforcement on motor timing is studied, a basic ability that requires temporal information processing. **Chapter 4** examines decision-making in the face of changing reinforcement contingencies. There is investigated whether children with ADHD are biased by the tendency to search for immediate reward while ignoring the aversive long-term outcomes of their choices. **Chapter 5** reports whether children with ADHD suffer from abnormalities in reinforcement learning. Children with ADHD were compared to typically developing children, as well as a clinical group to investigate the specificity of abnormal reinforcement sensitivity in ADHD. **Chapter 6** reports a study on heart rate responses to reinforcement. Both immediate changes (a measure of feedback monitoring) following reinforcement are reported as well as more slow changes in heart rate variability that are suggested to be indicative of mental effort. **Chapter 7** contains a general discussion of the findings, clinical implication as well as directions for future research. Finally, some concluding remarks are presented.

The current thesis aims to answer three main questions: Firstly, are neurocognitive dysfunctions in ADHD secondary to a motivational deficit such as an abnormal sensitivity to reinforcement contingencies? To answer this question, the impact of reinforcement is investigated on cognitive control (Chapters 2, 4 and 5) and temporal information processing (Chapter 3). Secondly, are children with ADHD sensitive to specific aspects of reinforcement that can explain the underlying mechanisms of a reinforcement deficit in ADHD? Do children with ADHD exhibit an aberrant sensitivity to: instances of reinforcement over feedback-only (e.g., Sergeant et al., 1999: Chapters 2, 3, 4, 5, and 6), the valence of reinforcement (e.g., Newman, 1987; Quay, 1988a; 1988b; 1988c; 1997; Sonuga-Barke, 2002; Wallace & Newman, 1990: Chapters 2, 3, and 6), the magnitude of reinforcement (Haenlein & Caul, 1989: Chapters 3, 4 and 5), or the frequency of reinforcement (Douglas, 1989; Sagvolden et al., 2005: Chapters 4 and 5)? Thirdly, is an abnormal sensitivity to reinforcement accompanied by abnormal autonomic responses to reward and penalty? To answer this question, heart rate and skin conductance responses (Chapters 2, 3, 4, and 6) as well as changes in heart rate variability are measured (Chapter 6).

Chapter 7

General Discussion: Limitations of a Motivational Explanation of ADHD

There is evidence that children with attention-deficit/hyperactivity disorder (ADHD) show motivational problems in terms of an abnormal response to reinforcement contingencies (e.g., Sonuga-Barke, Taylor, Sembi, & Smith, 1992; Tripp & Alsop, 1999), however, the nature of this problem is not well understood. The studies presented in this thesis aimed to extend the knowledge on the role of reinforcement in ADHD by studying neurocognitive as well as autonomic functions of children with ADHD and typically developing children. Three questions were investigated. Firstly, are neurocognitive dysfunctions in ADHD secondary to a motivational deficit such as an abnormal sensitivity to reinforcement? Secondly, are children with ADHD sensitive to specific aspects of reinforcement that can explain the underlying mechanisms of a reinforcement deficit? Thirdly, is an abnormal sensitivity to reinforcement accompanied by aberrant autonomic responses to reward and penalty?

ADHD: Can Reinforcement Resolve the Problem?

The first issue addressed in the current thesis was whether children with ADHD suffer from a reinforcement sensitivity problem that may interfere with their neurocognitive abilities. The majority of studies reviewed in Chapter 2 indicate that both reward and penalty positively influenced task performance as well as self-rated motivation in all children. Five out of ten studies, however, demonstrated a disproportional improvement in children with ADHD under contingency conditions (either reward or penalty) compared to a neutral condition. This suggests that the improvement in

performance, when coupled with reward or penalty was somewhat more prominent for children with ADHD than for typically developing children. No group differences were observed in increases in self-rated motivation, indicating that self-rated and observed motivation (improvements in task performance) did not tap the same concept. The experimental studies (Chapter 3, 4, 5 and 6) of this thesis confirmed that performance deficits in ADHD partly represent a motivational problem, as observed by an abnormal sensitivity to reinforcement. Thus, observed impairments of children with ADHD in cognitive control (response inhibition, decision making; Chapters 2 and 4), temporal information processing (Chapter 2 and 3), mathematics and visual matching (Chapter 2) diminished, when performance was reinforced immediately and frequently. Importantly, the abovementioned impairments of children with ADHD were not completely ameliorated by reinforcement contingencies: In most studies, performance of ADHD children remained inferior to that of controls (Chapters 2, 3, 5 and 6). Some performance deficits such as stimulus-response learning in ADHD (Chapter 5) may be insensitive to the reinforcement conditions. Thus, neurocognitive deficits in children with ADHD were partly explained by a motivational problem.

Motivational Modulation of Cognitive Control

In Chapter 2, children with ADHD compared to a typically developing group displayed a disproportional improvement in performance (collapsed over a range of cognitive tasks) in the face of reinforcement contingencies. Due to the heterogeneity in cognitive processes explored in Chapter 2, it was not possible to study the impact of reinforcement on specific neurocognitive deficits in ADHD. However, the inclusion of more recent studies on reinforcement and performance in ADHD allows investigation of the impact of reinforcement on response inhibition, an often reported cognitive control deficit in ADHD (e.g., Doyle et al., 2005; Willcut, Doyle, Nigg, Faraone, & Pennington, 2005). Two out of six studies on response inhibition indicated an abnormal reinforcement sensitivity in ADHD (Konrad, Gauggel, Manz, & Scholl, 2000; Slusarek, Velling, Bunk, & Eggers, 2001). In these two studies, reinforcement contingencies 'normalized' performance of children with ADHD to a level comparable to that of typically developing controls. The other studies, however, indicated that response inhibition problems in children with ADHD were independent of the reinforcement conditions (Crone, Jennings, & Van der Molen, 2003; Desman, et al., 2006; Scheres, Oosterlaan, & Sergeant, 2001; Wodka et al., 2007). Thus, the majority of studies demonstrated that inhibition problems in children with ADHD represented a stable deficit that was independent of motivational manipulations.

Motivational Modulation of Temporal Information Processing

Chapter 3 addressed whether temporal information processing deficiencies in ADHD were secondary to a motivational deficit. Children with ADHD persistently produced shorter, as well as more variable time intervals than typical developing controls, confirming earlier findings (Toplak, Dockstader, & Tannock, 2006). Systematic over- or underproduction of time is thought to indicate defect internal clock functioning (Harrington, Haaland, & Hermanowicz, 1998; Ivry, 1996). A fast internal clock in ADHD (systematic production of shorter time intervals) implies that time intervals subjectively 'lasts longer' for children with ADHD than for control children, which may explain the persistent problems with waiting (Sonuga-Barke, 2002; Sonuga-Barke et al., 1992) and disinhibited behaviour such as blurting out answers before a question has been completed. The internal clock dysfunction in the ADHD group was insensitive to motivational modulations, similarly to what has been reported by others (Van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005a). More variable time intervals in ADHD as observed in Chapter 3 would point towards impaired response organization. In contrast to internal clock functioning, timing variability in ADHD children reduced compared to controls, when performance was coupled to monetary consequences compared to feedback only (Chapter 3). This indicates that time production difficulties in ADHD partly represent a motivational problem. Bellgrove, Hester, and Garavan (2004) reported that greater response variability was associated with impaired performance on a go/no-go task, indicating that variability in responding may impair cognitive control functions such as response inhibition. In addition, there is evidence that controlling for 'basic' abilities (such as response variability) ameliorates differences in cognitive control between children with ADHD and typically developing children (Rhodes, Coghill, & Matthews, 2005; Marks, et al., 2005). Since enhanced variability in responding is reported often in ADHD (e.g., Leth-Steensen, Elbaz, & Douglas, 2001), our findings increase the understanding of the role of reinforcement in more complex neurocognitive deficiencies in ADHD. Therefore, future studies should include measures of more 'basic' functions, such as response variability, when studying the role of reinforcement in ADHD.

Thus, the first main question in this thesis, whether neurocognitive dysfunctions in ADHD are secondary to a motivational deficit such as aberrant reinforcement sensitivity, cannot be confirmed. The findings indicate that only some (aspects of) neurocognitive abilities in ADHD are sensitive to reinforcement contingencies. Performance deficits in children with ADHD cannot be fully attributed to a motivational deficit. This agrees with the suggestion that there are multiple distinct endophenotypes of ADHD, among which, an aberrant sensitivity to reinforcement (Doyle et al., 2005; Castellanos & Tannock, 2002; Nigg, 2005; Sonuga-Barke, 2002).

Sensitivity to Specific Aspects of Reinforcement: Towards a Clearer Definition of ADHD?

The second question in this thesis was whether children with ADHD may be sensitive to specific aspect of reinforcement such as suggested by several theoretical models (Barkley, 1997; Douglas, 1989; Haenlein & Caul, 1987; Quay, 1988a; Sagvolden, Johansen, Aase, & Russell, 2005; Sergeant, Oosterlaan, & Van der Meere, 1999; Sonuga-Barke, 2002). There was investigated whether children with ADHD compared to typical developing children displayed an abnormal sensitivity to: reinforcement compared to feedback only (Chapters 2, 3, and 6), the valence of reinforcement (Chapters 2, 3, and 6), the frequency of reinforcement (Chapters 4 and 5) or the magnitude of reinforcement (Chapters 3, 4 and 5).

Compared to controls, children with ADHD seem somewhat more sensitive to monetary reinforcement than controls (as described in the section above). No evidence was revealed for an abnormal sensitivity in children with ADHD to the valence of reinforcement (Chapters 2, 3, and 6). One exception was that, compared to typical developing controls, children with ADHD exhibited a decreased sensitivity to behavioural choices that were ultimately disadvantageous (Chapter 4). In this study, children had to choose between three alternatives: A favourable alternative that carried small gains and small losses, and two unfavourable alternatives that both carried large losses, but were dissociated by the size of their gain, being either small or large. By choosing repeatedly between the alternatives, children had to find out that the favourable alternative resulted in the largest net gain (gains larger than losses). In other words, children had to remember the reinforcement history of the alternatives. Since it was too difficult to calculate the exact net gain of the alternatives, children had to use their 'gut-feeling' to experience what alternative was ultimately favourable (Damasio, 1996). Children with ADHD showed a maladaptive response strategy by choosing less often for the advantageous alternative and more often for the disadvantageous alternatives. This was independent of whether the gain in the disadvantage alternative was large or small. These findings suggest that children with ADHD were less sensitive than controls to future negative consequences, rather than focussing on immediate gains (e.g., Newman, 1987). This indicates that children with ADHD displayed difficulties keeping track of the reinforcement history of the task. Possibly, the decay of the impact of aversive stimuli was faster in children with ADHD than in typically developing children. This was emphasized by the findings in Chapter 4 that decision-making problems in ADHD diminished, when penalty (carried by the unfavourable alternatives) was delivered more frequently, thus less distant in time. A possible faster decay of reinforcement in ADHD has been suggested earlier with re-

spect to reward processing; children with ADHD would suffer from a faster decay of reward as the result of a dysfunction in dopamine transmission in the limbic system (Johansen, Aase, Meyer, & Sagvolden, 2002). This diminished sensitivity to aversive behavioural consequences may be regulated by the neurotransmitter serotonin and noradrenalin (Quay, 1988a; 1988b; 1988c; 1997). According to Quay, due to this neurochemical imbalance, children with ADHD suffer from a decreased control over behaviour by signals of non-reward or punishment and show increased disinhibited behaviour (Gray, 1982; 1987). The results of this thesis suggest that children with ADHD were sensitive to penalty like controls, when penalty was delivered immediately and consistently (Chapter 3, 4, and 6), in line with other studies (Daugherty & Quay, 1991; Fischer, Barkley, Smallish, & Fletcher, 2005).

Children with ADHD and typical developing children were differentiated by their sensitivity to the frequency of reinforcement (Chapters 4 and 5). In the decision making study (Chapter 4) performance of children with ADHD improved to a level similar to that of controls when reinforcement (penalty) was delivered frequently versus infrequently, suggesting a diminished sensitivity to low frequency reinforcement. In contrast, in the reinforcement learning task (Chapter 5) infrequent compared to frequent rewards improved performance of typically developing children, while this was not seen in children with ADHD. It was speculated that, in line with earlier suggestions (Sergeant et al., 1999; Van der Meere, 2002), that children with ADHD were hypo-aroused and less sensitive to the possible (over)arousing impact of frequent rewards (see discussion of Chapter 5).

Children with ADHD do not seem to profit like typically developing children from a large compared to a small magnitude of reinforcement (Chapters 3, 4 and 5). These findings question the assumptions of an elevated reward threshold in ADHD (Haenlein & Caul, 1987).

Thus, the second question of this thesis, whether children with ADHD and typical developing children differed in their sensitivity to specific aspects of reinforcement was confirmed: Children with ADHD were differentiated from controls by an aberrant sensitivity to reinforcement versus feedback-only and an aberrant sensitivity to the frequency (or immediacy) of reinforcement. When delivered frequently and immediately, both reward and penalty seemed effective in decreasing performance deficits in children with ADHD to a level similar to that of typical developing controls (Chapters 2, 3, and 6). This suggests that children with ADHD may suffer from a motivational deficiency when reinforcement is not available (Barkley, 1997; Douglas, 1989; Sergeant et al., 1999). This would result in a disability to adjust their behav-

ioural strategy and increase the allocation of attention that is necessary to keep up with the demands of the task (Sergeant et al., 1999; Van der Meere, 2002). In face of external stimulation, such as monetary gain and loss, children with ADHD seem able to improve their performance similarly to typically developing children. A recent study (Geurts, Luman & Van Meel, unpublished) demonstrated that not only monetary reinforcement but also social motivators (playing a game against other children) can ameliorate performance deficits of children with ADHD in a task that measured interference control.

Autonomic Response to Reinforcement Contingencies

The third question here was to investigate whether an abnormal sensitivity to reinforcement in children with ADHD may be linked to abnormalities in the autonomic nervous system (ANS). The studies in this thesis revealed heterogeneous results.

The studies showed some evidence of abnormal sympathetic nervous system (SNS) activity to feedback stimuli in children with ADHD compared to typical developing controls, when their performance was not reinforced (Chapter 3, 4, and 6). The autonomic response to feedback in children with ADHD 'normalized' when performance was coupled to monetary contingencies. Interestingly, normalization of autonomic responses in the ADHD group was accompanied by a normalization of their performance. In the timing study (Chapter 3), both skin conductance responses (to feedback) as well as timing variability of ADHD children normalized to a level similar to controls when reinforcement was added to feedback. In the decision-making study (Chapter 4), skin conductance responses following unfavourable choices as well as performance of children with ADHD normalized compared to typically developing controls, when penalties were delivered frequently versus infrequently. Increased skin conductance responses in children with ADHD as observed in the reinforcement conditions might be related to an increase in the awareness of the consequences of feedback (see discussion of Chapter 3). This could explain the disproportional increase in performance in children with ADHD when feedback was coupled to reinforcement. Decreases in low frequency heart rate variability (associated with an increase in task engagement, Chapter 6), when reinforcement was added to feedback, were found to be larger in children with ADHD than in controls (Chapter 6). Changes in low frequency heart rate variability have been associated with activity in the vascular system that initiates changes in blood flow that are necessary for local metabolic demands (Akselrod et al., 1985). These findings suggest that monetary reinforcers increase the allocation of attention in children with ADHD, which improves performance.

And although performance of children with ADHD improved, when reinforcement was added to feedback, it remained inferior to that of controls (Chapter 6). Possibly, children with ADHD had to compensate for deficits that are not solely a motivational dysfunction (in this case timing performance, see Chapter 3).

Some evidence was found for smaller (phasic) heart rate and skin conductance responses to reinforcement in children with ADHD compared to in typically developing controls, suggesting stronger parasympathetic than sympathetic activity in ADHD (Chapter 2: Crone, Jennings, & Van der Molen, 2003; Iaboni, Douglas, & Ditto, 1997). These findings are in line with a more recent study that showed smaller cardiac activity to reward in children with ADHD compared to typically developing children (Crowell et al., 2006). The experimental chapters in this thesis, however, did not report on abnormal autonomic responses to reinforcement contingencies in ADHD (Chapter 3, 4, and 6), with the exception of one study that found enlarged HR responses to reward in the ADHD group (Chapter 4). Thus, children with ADHD exhibited abnormal cardiac responses to reward, showing either a blunted or increased response compared to typically developing children.

Moreover, the studies in this thesis show some evidence for an aberrant autonomic response in children with ADHD to reinforcement contingencies, confirming the third research question of this thesis. Children with ADHD were differentiated from controls in their autonomic response to reinforcement compared to feedback only (Chapter, 2, 3, 4, and 6) and the frequency of reinforcement (Chapter 4). There were some indications of an abnormal cardiac response to reward stimuli in ADHD; no strong evidence was found for an abnormal response to penalty. The exact relation between performance problems and autonomic responses remains unclear, since the correlations between the two levels of measurement were weak.

Limitations

Before conclusions are drawn regarding the role of reinforcement in ADHD, some limitations are worth noting. A first limitation is the comorbidity in ADHD with other developmental disorders that may influence the sensitivity to reinforcement. For example, all ADHD groups described in the current thesis show comorbid antisocial behaviour, such as observed in oppositional defiant disorder (ODD) or conduct disorder (CD). The presence of comorbid ODD and CD in our group samples is in line with observations in large community samples (Angold, Costello, & Erkanli, 1999). Anti-social behaviour has been related to poor self-regulation in face of reinforcement

(Newman & Wallace, 1993; Raine, 1993): Raine proposed that a lack of fear in antisocial children decreases the attention to threat related stimuli such as punishment, and prevents passive avoidance learning. There are several studies that support this suggestion (Daugherty & Quay, 1991; Fonseca & Yule, 1995; Matthys, Van Goozen, De Vries, Cohen-Kettenis, & Van Engeland, 1998; Shapiro, Quay, Hogan, & Schwartz, 1988). Internalizing behaviour problems (high fear levels) ameliorated impaired performance of antisocial children on reinforcement tasks (O'Brien & Frick, 1996) and may possibly do the same in children with ADHD, in line with a recent decision making study in ADHD (Garon, Moore, & Waschbusch, 2006). Otherwise, children with autism spectrum disorder (ASD) may show overlap with ADHD children in their response to reinforcement contingencies (see Chapter 5). The impact of reinforcement on children with learning problems (highly comorbid in ADHD), for example, has not been investigated thus far. To minimize the impact of comorbid symptoms in the studies described in this thesis, children with a clinical diagnosis other than ADHD, ODD or CD were excluded from the ADHD group, such as anxiety disorder, depression disorder, or ASD. In the experimental studies of this thesis, the contribution of the ODD and CD symptoms to the impact of reinforcement on performance in ADHD was statistically non-significant (Chapter 3, 4 and 6). Clearly, future studies with large sample sizes are needed that focus on the specificity of motivational problems in ADHD.

A second issue is that motivation in the current thesis was manipulated using monetary reinforcers. There was no control over other possible motivating factors, such as the impact of computerized tasks, exiting test stimuli, the individualized test situation, and the fact that most children were free from school to come over to the university test lab. Possibly, these background factors may have increased the motivational drive to perform well during the experiments, which may have overestimated the performance of children with ADHD. Otherwise, some tasks may have been extremely boring for children to perform, resulting in impaired performance in the ADHD group. Systematic investigation of impact of reinforcement on performance outside the lab requires longitudinal observation studies and large sample sizes. In the current thesis, the impact of background factors that could influence the level of motivation was minimized by manipulating various reinforcement conditions within each subject.

Third, the absence of strong correlations between the autonomic responses and performance in face of reinforcement contingencies in ADHD may weaken our speculations on the relation between psychophysiological processes and performance. Possibly, an abnormal sensitivity to reinforcement in ADHD in terms of performance and autonomic responses are caused by similar deficiencies in the brain, but share no

causal relation. Several brain structures that are associated with autonomic responses to affective stimuli are also associated with neurocognitive functioning, such as the anterior cingulate cortex (ACC), the ventromedial prefrontal cortex (VMedPFC), the ventral striatum and the amygdala (Anderson et al., 2003; Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Damasio, Damasio, & Lee, 1999; Beauchaine, 2001; Bush, Luu & Posner, 2000; Critchley, Matthias, & Dolan, 2001; Critchley et al., 2003). These brain structures have been found to function abnormally in ADHD (Bush et al., 1999; Ernst et al., 2003; Fallgatter et al., 2004; Plessen et al., 2006; Scheres et al., 2007). Low correlations between different levels of investigations have been observed more often in ADHD (e.g., Van Meel et al., 2005a; Van Meel et al., 2005b). Therefore, future multi-level projects are needed to resolve the discrepancies between the various levels of research (e.g., performance, psychophysiology, neuroanatomy, genetics, animal and computational models). Such integrated projects, however, cope with difficulties in the recruitment of children, and may result in biased samples.

General Conclusions and Future Directions

Children with ADHD showed a disproportional improvement in neurocognitive functioning compared to typically developing children, when performance was coupled to immediate and consistent monetary consequences. These findings suggest that children with ADHD suffer from a motivational deficit (Barkley, 1997; Douglas, 1989; Sergeant et al., 1999). Children with ADHD exhibited a disability to adjust their behavioural strategy and increase the attentional effort that is necessary to keep up with environmental demands without the help of external reinforcement (e.g., Chapter 3, Konrad et al., 2000; Slusarek et al., 2001). Although performance of ADHD children improved to a larger extent than that of controls, when reinforcement was available, in most studies it remained inferior to that of typically developing children. This indicates that neurocognitive deficits in ADHD are not secondary to a motivational deficit, *rejecting our first research question*. Performance in ADHD seemed impaired by several neurocognitive dysfunctions such as difficulties in reinforcement processing, cognitive control (Chapters 2, 4 and 5) and temporal information processing (Chapter 3). These dysfunctions may represent distinct, but interrelated, developmental pathways to ADHD, as described in the introductory chapter (Castellanos & Tannock, 2002; Nigg, 2005; Sonuga-Barke, 2002).

Interestingly, some evidence was found that basic abilities in ADHD such as timing variability are susceptible to disproportional improvement when coupled to monetary contingencies (Chapter 3). Since these basic abilities play a major role in performance

on more complex tasks (Bellgrove, Hester, & Garavan, 2004), more insight into how reinforcement influences these basic abilities is essential. Time production involves the activation of subcortical structures such as the cerebellum (Harrington et al., 1998; Ivry et al., 2002), which is found to correlate positively with the persistency of ADHD symptoms (Mackie et al., 2007) and may be characteristic for ADHD (Durston et al., 2004). Future studies should therefore systematically explore the impact of reinforcement on basic as well as more complex neurocognitive functions.

The results regarding *the second question of this thesis*, whether children with ADHD were sensitive to specific aspects of reinforcement, demonstrate that ADHD children were differentiated from controls by their sensitivity to reinforcement versus feedback-only and by their sensitivity to reinforcement frequency. No evidence was revealed that children with ADHD profited more than typically developing children from changes in the magnitude of reinforcement, arguing against the suggestion that children with ADHD suffer from an elevated reward threshold (Haenlein & Caul, 1987). Some evidence was found that children with ADHD compared to typically developing children are less sensitive to aversive consequences of behaviour, specifically when penalty was delivered infrequently compared to frequently (Chapter 4). Possibly, the decay of penalty is faster in ADHD compared to typically developing children. According to Sagvolden et al. (2005) the behaviour that characterizes ADHD can be explained by a hypo-dopaminergic functioning in the fronto-striatal pathway that is responsible for a faster decay of the impact of anticipated rewards. A recent imaging study demonstrated that children with ADHD compared to controls showed less ventral striatum activation during reward anticipation (Scheres et al., 2007), supporting the suggestion that the saliency of anticipated rewards is diminished (Johansen et al., 2002; Volkow et al., 2004). This may explain the finding that children with ADHD are more influenced by the last reward received than by the reinforcement history (Tripp & Alsop, 1999). Clearly, more studies are needed to confirm that children with ADHD are less sensitive to the reinforcement history of penalty, similarly to reward (Rapport, Tucker, DuPaul, Merlo, & Stoner, 1986; Sonuga-Barke et al., 1992; Tripp & Alsop, 1999). If a decreased sensitivity to aversive consequences is related to a weak behavioural inhibition system (e.g., Quay, 1988a) future studies need to determine whether inhibition problems in ADHD correlate with a decreased sensitivity to memorable signals of punishment. In contrast, when delivered immediately and consistently, children with ADHD were sensitive to reward and penalty, similarly to controls.

Reinforcement deficiencies in the dopamine system of the limbic system, such as suggested in ADHD (Johansen et al., 2002), have been related to addictive behaviours

including drinking, drug abuse, and gambling (Blum et al., 2000). People with addiction problems are suggested to require more dopamine than persons without this reward deficiency, which leads to reward-seeking behaviour (Goudriaan, 2005). Dopamine receptor abnormalities have been associated with reward searching behaviours (Blum et al., 1996; Comings & Blum, 2000) as well as aggression problems (Chen et al., 2007) and possibly, the same genes are associated with ADHD (Waldman & Gizer, 2006). The risk of children with ADHD to develop aggressive and addictive behaviour during adolescence and adulthood is considerable (Biederman, Monuteaux et al., 2006; Sood, Pallanti, & Hollander, 2003). Therefore, future longitudinal approaches are needed that focus on the behavioural consequences of an abnormal sensitivity to reinforcement in children with ADHD, as observed in the current thesis.

The third research question, whether there is a physiological basis of motivational problems in children with ADHD, *could not be confirmed or rejected*. There is some evidence that children with ADHD show abnormal cardiac activity to reward, pointing to abnormal SNS activity. No strong evidence was found for the suggestion that children with ADHD show attenuated autonomic activity to aversive stimuli that may explain disinhibition problems in ADHD (Newman, 1987; Patterson & Newman, 1993; Quay; 1988a; 1988b; 1988c; 1997; Wallace & Newman, 1990). Abnormal autonomic activity (increased heart rate variability and lower skin conductance responses) as well as low performance of children with ADHD 'normalized' when reinforcement was added to performance feedback (Chapters 3, 4 and 6). When reinforcement is not available, children with ADHD seem to suffer from a defect to activate efficiently the autonomic system, in response to changing environmental demands or internal goals. An increases in awareness of the consequences of behaviour (Chapter 3 and 4) and an increases in the motivation to perform well when reinforcement is available (Chapter 6), may explain the dependence of children with ADHD on contingencies to optimize their performance (Chapters 2, 3, and 4).

If the impact of reinforcement in children with ADHD decays faster than in controls, future studies should track the physiological response to reinforcement over time. The relatively slow changes in SNS activity in terms of skin conductance (around 0.2 Hz) or heart rate variability (around 0.06 Hz) are inadequate to detect such decay. In a recent electroencephalographic (EEG) study, children with ADHD displayed larger ERPs to penalty than controls in an early processing phase, while showing smaller ERPs to penalty in a later phase that is related to the affective evaluation of stimuli (Van Meel et al., 2005b). Thus, future ERP studies are needed to confirm the possibility that children with ADHD profit optimally from reinforcement when it is delivered immediately and frequently.

Motivational modulation of performance in children with ADHD as demonstrated in this thesis emphasizes the importance of behavioural interventions that make use of reinforcement contingencies. Contingency programmes that involve the direct application of both positive reinforcement and response cost (or time-out) are found to be effective in decreasing 'off-task' (or task irrelevant) behaviour in children with ADHD (DuPaul, Guevremont & Barkley, 1992; McGoey & DuPaul, 2000; Rapport, Murphy & Bailey, 1982). If children with ADHD are able to meet increasing task demands, when they are motivated by external reinforcement, studies are needed to explore which environmental conditions may optimize their abilities. The results of this thesis suggest that, when reinforcement is delivered immediately (Chapters 2, 3, and 6) and frequently (Chapter 4), both reward and penalty may improve (motor) behaviour and cognitive abilities of children with ADHD. However, future clinical studies are needed to confirm these suggestions.

Children with ADHD may be extremely vulnerable to exhibit an abnormal response to contingencies due to their learning history of the motivation to perform well (Chang & Burns, 2005). During development, children with ADHD are confronted with their cognitive and motor disabilities and children with ADHD may suffer from social rejection as a result of their uncontrolled behaviour (De Boo & Prins, 2007). These experiences may have decreased their motivation to perform well in school or behave well at home. No studies have investigated the impact of these social factors on motivational problems in ADHD. The prefrontal cortex of humans is developing until late adolescence (e.g., Segalowitz & Davies, 2004) and future studies may focus on the impact of early life events on the prefrontal cortex that may influence the development of motivational problems in ADHD.

To Conclude, This Thesis Suggests That:

- Immediate and frequent monetary reinforcement may normalize performance of children with ADHD. However, more replication studies are needed that systematically investigate the impact of reinforcement on neurocognitive functioning in ADHD. Some neurocognitive difficulties of ADHD children seem sensitive to motivational modulation, while others seem more stable. If replicated, such findings would have important therapeutic implications.

- Multi-level studies into ADHD are needed that explore relation between physiological and performance deficits in order to understand the underlying mechanisms of an abnormal sensitivity to reinforcement. The autonomic abnormalities in ADHD suggest an impaired awareness of the affective consequences of behaviour. This may explain the need for external (monetary) stimulation to perform optimally. If replicated, heart rate and skin conductance measures should be explored as diagnostic tools.

- If children with ADHD are less sensitive to reinforcers that are more distant in time, they need to be reinforced immediately and frequently for their behaviour, rather than more intensely. Future studies are needed to investigate the impact of more distant reinforcement on the performance of children with ADHD. In addition, psychophysiological studies are needed that track the physiological response of children with ADHD to reinforcement over time.

- Future studies should focus on the clinical specificity of an abnormal reinforcement sensitivity in ADHD, since this thesis shows evidence of such problems in comorbid groups of ADHD. More knowledge on the impact of reinforcement on different comorbid groups of ADHD would increase the specificity of interventions (such as contingency training) for these various clinical subgroups.

- More knowledge on the development of an abnormal sensitivity to reinforcement in ADHD is required. Studies are needed that investigate whether early intervention can ameliorate the development of an abnormal reinforcement sensitivity in ADHD. This may help to prevent the development of behavioural problems in adolescence and adulthood.